09/669793
530

PATENT COOPERATION TREATY

50c2

PCT

From the INTERNATIONAL BUREAU

To:

JORRITSMA, Ruurd
Nederlandsch Octrooibureau
Scheveningseweg 82
P.O. Box 29720
NL-2502 LS The Hague
PAYS-BAS

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

Date of mailing (day/month/year)
26 July 2001 (26.07.01)

Applicant's or agent's file reference
BO 42384

IMPORTANT NOTIFICATION

International application No.
PCT/NL00/00042

International filing date (day/month/year)
20 January 2000 (20.01.00)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address
HAGEMAN, Robert, Johan, Joseph
Weidezoom 52
NL-2742 EV Waddinxveen
Netherlands

State of Nationality: NL
State of Residence: NL
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
HAGEMAN, Robert, Johan, Joseph
Hamsterlaan 12
NL-6705 CT Wageningen
Netherlands

State of Nationality: NL
State of Residence: NL
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
Anman QIU

Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

004177595

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 27 September 2000 (27.09.00)	
International application No. PCT/NL00/00042	**Applicant's or agent's file reference** BO 42384
International filing date (day/month/year) 20 January 2000 (20.01.00)	**Priority date** (day/month/year) 20 January 1999 (20.01.99)
Applicant HAGEMAN, Robert, Johan, Joseph et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

16 August 2000 (16.08.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Olivia TEFY
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
BO 42384		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/NL 00/00042	20/01/2000	20/01/1999
Applicant		
N.V. NUTRICIA et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. ---

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NL 00/00042

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 15 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
P[redacted]L 00/00042

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/505 A61K31/44 A61K38/41 A23L1/302

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A23L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 545 670 A (S.H.BISSBORT ET AL.) 13 August 1996 (1996-08-13) claims ---	1,15
X	DE 43 26 675 A (MEDICE CHEM.-PHARM.FABRIK PÜTTER) 16 February 1995 (1995-02-16) claims ---	1,15
X	US 5 292 538 A (S.M.PAUL ET AL) 8 March 1994 (1994-03-08) column 1, line 15-26; claims 1,6 ---	1,2,4
X	US 5 631 271 A (W.J.SERFONTEIN) 20 May 1997 (1997-05-20) claims 1,12 ---	1-3
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 April 2000	29. 05. 2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Van Moer, A

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
[redacted]NL 00/00042

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 721 742 A (CLINTEC) 17 July 1996 (1996-07-17) claims	1-15

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IL 00/00042

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5545670 A	13-08-1996	AP 387 A	31-07-1995
		AU 666490 B	15-02-1996
		AU 2352792 A	18-03-1993
		CA 2078019 A	14-03-1993
		EP 0532369 A	17-03-1993
		IL 103152 A	16-08-1998
DE 4326675 A	16-02-1995	NONE	
US 5292538 A	08-03-1994	AU 669003 B	23-05-1996
		AU 4992893 A	14-02-1994
		EP 0651617 A	10-05-1995
		WO 9402036 A	03-02-1994
US 5631271 A	20-05-1997	US 5254572 A	19-10-1993
		EP 0379936 A	01-08-1990
		JP 2237921 A	20-09-1990
		ZA 9000319 A	25-09-1991
		AU 8169087 A	02-06-1988
		EP 0270026 A	08-06-1988
		JP 63145229 A	17-06-1988
		NZ 222664 A	26-06-1990
		ZA 8708981 A	25-04-1990
		CA 2105881 A	15-03-1994
		CN 1087522 A	08-06-1994
		EP 0595006 A	04-05-1994
		JP 6192104 A	12-07-1994
		ZA 9306724 A	14-08-1995
EP 721742 A	17-07-1996	US 5589468 A	31-12-1996
		AU 4076595 A	25-07-1996
		CA 2166003 A	14-07-1996
		JP 8231411 A	10-09-1996
		US RE36288 E	31-08-1999
		US 5686429 A	11-11-1997

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

To:

JORRITSMA, Ruurd
Nederlandsch Octrooibureau
Scheveningseweg 82
P.O. Box 29720
NL-2502 LS The Hague
PAYS-BAS

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

Date of mailing (day/month/year) 10 April 2000 (10.04.00)	
Applicant's or agent's file reference BO 42384	**IMPORTANT NOTIFICATION**
International application No. PCT/NL00/00042	International filing date (day/month/year) 20 January 2000 (20.01.00)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 20 January 1999 (20.01.99)
Applicant N.V. NUTRICIA et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An **asterisk(*)** appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The **letters "NR"** appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
20 Janu 1999 (20.01.99)	99200166.9	NL	22 Marc 2000 (22.03.00)
29 Apri 1999 (29.04.99)	99201359.9	NL	22 Marc 2000 (22.03.00)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

Taïeb Akremi

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

To:
JORRITSMA, Ruurd
Nederlandsch Octrooibureau
Scheveningseweg 82
P.O. Box 29720
NL-2502 LS The Hague
PAYS-BAS

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

Date of mailing (day/month/year) 27 July 2000 (27.07.00)	
Applicant's or agent's file reference BO 42384	**IMPORTANT NOTICE**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/NL00/00042	20 January 2000 (20.01.00)	20 January 1999 (20.01.99)

Applicant
N.V. NUTRICIA et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,JP,KP,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CN,CR,CU,CZ,DE,DK,DM,EA,EE,EP,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   27 July 2000 (27.07.00) under No. WO 00/43013

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra

Telephone No. (41-22) 338.83.38

Continuation of Form PCT/IB/308

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

Date of mailing (day/month/year)	IMPORTANT NOTICE
27 July 2000 (27.07.00)	
Applicant's or agent's file reference	**International application No.**
BO 42384	PCT/NL00/00042

The applicant is hereby notified that, at the time of establishment of this Notice, the time limit under Rule 46.1 for making amendments under Article 19 has not yet expired and the International Bureau had received neither such amendments nor a declaration that the applicant does not wish to make amendments.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
BO 42384		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/NL00/00042	20/01/2000	20/01/1999
International Patent Classification (IPC) or national classification and IPC A61K31/505		
Applicant N.V. NUTRICIA et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of X sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☐ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16/08/2000	22.03.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Toulacis, C Telephone No. +49 89 2399 8638

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/NL00/00042

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-15 as originally filed

Claims, No.:

1-15 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)
see separate sheet

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 1-15.

because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

   ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1-15 are so unclear that no meaningful opinion could be formed (*specify*):
   see separate sheet

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

I

The amendments filed with the letter of 23.02.2001, introduce subject-matter which extends beyond the content of the application as filed, contrary to Art. 34 (2) b) PCT.

The amendments concerned are the following:

"... and at least one component selected from riboflavin, thiamine, niacin and zinc..." in claims 1, 14 and 15.

The scope of claims 1 to 15 has therefore been extended. No basis for such an extension can be found in the application as filed; the requirements of Art. 34 (2) b) and Rule 70.2 (c) PCT are not met.

In this context reference is made to the Guidelines for examination in the PCT (Chapter VI, 7.9 and 7.10)

Furthermore, Applicant's attention is drawn to the fact that the necessary features cannot be taken into a claim from the examples or figures, since the examples or figures are only specific embodiments, wherein a claim is a generalisation.

III

1. The subject-matter of claims 1 to 15 of the present application is not clear (Art. 6 PCT).

1.1 According to the description of the present Application the <u>combination</u> of folic acid, vitamin B6 and B12 is crucial for the treatments claimed.
The wording of claims 1, 14 and 15 does not exclude the separate use of said vitamins. Thus, said claims are not clear and not supported by the description.
The same applies to the dependent claims 2 to 13.

1.2 The expressions "... their functional analogues..." in claim 1 and "... niacin equivalents... " in claim 13, are not clear.

1.3 The expression "... per 100 kcal..." in claims 5-8, 10, 14 defining a composition, is not clear. It is not apparent which components deliver said 100 kcal in the claimed compositions.

1.4 According to claim 13, the composition is defined by comprising certain amounts of the components per daily dosage. Said daily dosage, however, is not defined. Thus, the scope of claim 13, is rendered unclear.

2. Concerning the use of the combination of folic acid, vitamin B6 and B12 for the manufacture of a pharmaceutical composition for the treatment of the conditions as defined in claim 1, the following is pointed out:

Document US-A-5 545 670 (D1) discloses a composition comprising the claimed combination of folic acid, vitamin B6 and B12, and a method for the treatment of myalgic encephalomyelitis known as chronic fatigue syndrome or stimulate the immune response system, or suppress allergic reactions(D1; abstract; column 1, line 9; column 4, lines 21-47).

Document DE-A-4 326 675 (D2) discloses the use of the combination of folic acid, vitamin B6 and B12 in the treatment or prevention of nerve degeneration disorders and senile dementia (D2; page 4, lines 35-38, 60-67; page 5, lines 1-10)

Document US-A-5 292 538 (D3) discloses sustained energy and anabolic compositions comprising a blend of simple sugars and more complex carbohydrates and said combination of vitamins for the treatment of many disorders resulting from negative energy balance and muscle catabolism (D3; column 1, lines 15-26; claims 1,6).

Document US-A-5 631 271 (D4) discloses compositions comprising vitamin B6, folate and vitamin B12, for the treatment and prophylaxis of metabolic disturbances in infants.

Document EP-A-0721 742 (D5) also discloses compositions comprising vitamin B6, folate and vitamin B12 for providing nutrition to elderly patients (D5; claims 3,5)

Said disclosures of D1-D5, would take away the novelty of the use as mentioned above and also of a product claim referring to a composition which comprises said vitamin combination.

In this context, it is pointed out that, the treatment of the pathological conditions mentioned in D1-D4, inherently improve the disorders or conditions as defined in claim 1 of the present application.

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* BO 42384

Box No. I TITLE OF INVENTION

PHARMACEUTICAL COMPOSITIONS FOR ALLEVIATING DISCOMFORT

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

N.V. Nutricia
P.O. Box 1
NL-2700 MA ZOETERMEER
the Netherlands

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(that is, country)* of nationality: the Netherlands (NL)

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This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

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Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ■ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

JORRITSMA, Ruurd et al
Nederlandsch Octrooibureau
Scheveningseweg 82, P.O. Box 29720
NL-2502 LS THE HAGUE
THE NETHERLANDS

Telephone No. 70 3527500

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BINDELS, Jacob Geert
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the Netherlands

This person is:
[ ] applicant only
[X] applicant and inventor
[ ] inventor only *(If this check-box is marked, do not fill in below.)*

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Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) 20 January 1999	99200166.9		European Patent Office RIJSWIJK (NL)	
item (2) 29 April 1999	99201359.9		" "	
item (3)				

☐ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): _____

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Date (day/month/year)	Number	Country (or regional Office)
4 November 1999	99201359.9	Europe

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets**:

request	:	4
description (excluding sequence listing part)	:	15
claims	:	2
abstract	:	1
drawings	:	
sequence listing part of description	:	
Total number of sheets	:	22

This international application is **accompanied by** the item(s) marked below:

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Figure of the drawings which should accompany the abstract:

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Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

JORRITSMA, R.

Nederlandsch Octrooibureau, The Hague, ~~20~~ January 2000

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FEE CALCULATION SHEET

Annex to the Request

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International application No.

Date stamp of the receiving Office

Applicant's or agent's file reference: BO 42384

Applicant: N.V. Nutricia

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE . . . . . 110 [T]

2. SEARCH FEE . . . . . 2082 [S]

International search to be carried out by EPO

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first 30 sheets . . . . . 901 [b1]

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Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PHARMACEUTICAL COMPOSITIONS FOR ALLEVIATING DISCOMFORT

(57) Abstract

The invention relates to products for complete nutrition of infants or diseased or elderly persons. The products are characterised by increased levels of folic acid, vitamin B6 and vitamin B12 or their functional equivalents. These products improve feelings of well–being of infants, especially those of young age, and are useful in the treatment and prevention of diseases that are associated with disorders of serotonin and melatonin metabolism.

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Pharmaceutical compositions for alleviating discomfort

Field of the invention

[0001] The invention is related to pharmaceutical and/or nutritional compositions, including infant formulae, for improving feelings of well-being, compensation of immaturity and problems in the metabolic capacity. The nutritional products provide complete nutrition to infants, diseased and elderly people, and their composition is characterised by increased amounts of cofactors. The nutritional products can also be in the form of supplements that provide the cofactors and only a part of the further desirable food components.

Background of the invention

[0002] At present a large part of the population of babies in industrialised countries are fed with specialised infant formulae. It has been reported that consumption of these formulae is associated with several medical problems, such as increased frequency of gastrointestinal problems and decreased immune status. Such problems may occur at young age, but perhaps also at later age, because infants that are exclusively fed with human breast milk would score better on these parameters. It has also been reported that infants that are exclusively fed with these artificial formulae suffer from longer episodes of crying compared to those that are fed with human breast milk. This suggests a general feeling of discomfort due to perhaps hunger, pain or even medical problems. These problems may delay development of the child and produce concerns and practical problems to the parents.

[0003] In a first aspect of the invention it is aimed to develop a new infant formula for complete nutrition that decreases the number of crying episodes and promotes sleeping behaviour for the child, especially for infants of young gestational age.

[0004] In a second aspect it is also aimed to develop infant formulae that compensate for the relatively small capacity of the (rapidly developing) metabolic systems of the child shortly after birth. This leads to improved health, formation of higher quality new tissue (visual acuity, intellectual capacities, etc.), a better immune status and a decrease in occurrence of periods of increased bilirubin plasma levels (hyperbilirubinaemia or jaundice). Increased bilirubin levels are known to occur relatively often within the first 3 weeks after birth. Some of the negative effects of this disorder have been described in the

prior art, including the inhibition by bilirubin of the uptake of the neurotransmitters dopamine and glutamate by the synaptic vesicles and the neurotoxic effects that this disease state may have.

[0005] Conventional infant formulae have been developed that mimic the composition of human breast milk to a degree that can be achieved at a reasonable price. These formulae are normally based on cow's milk proteins like casein or mixtures of casein and whey. In case of problems, such as metabolic disorders or allergic reactions, other protein sources are used like hydrolysates or soybean proteins; alternatively the allergic component is replaced by another non-allergenic ingredient. However, the composition of these formulae still differs from that of human breast milk. The relatively low levels of tryptophan and cysteine/cystine can be compensated for by increasing the amount of protein in the product. However, this increases the amount of threonine to very high levels and increases the costs of the formulae. Also the imbalances with regard to the ratio of tryptophan to the sum of the large neutral amino acids will be maintained.

[0006] In a further aspect, the invention is related to the use of folic acid, vitamins B12 and B6 or their functional analogues in the manufacture of compositions for the prevention and/or treatment of specific neurological disorders. The invention also covers the products that are obtained by such use. Products according to the invention will be effective in improving sleep behaviour, insomnia, mood, decrease feelings of fear and depression and increase feelings of wellbeing. In addition, undesirable symptoms related to neurodegenerative disorders like Alzheimer, Parkinson and schizophrenia are decreased. Also, the products can be helpful in the prevention and/or treatment of symptoms associated with restless legs syndrome, myoclonus (a disorder that is often accompanied by muscle contractions and seizures), Gilles de la Tourette, phenylketonuria, multiple sclerosis, analgesia, epilepsy, mania, aggressive behaviour, bulimia and other disorders associated with saturation feelings after eating, ADHD, and psychiatric disorders associated with ageing. Large parts of the population suffer from one of these disorders. Application of common drug therapy may result in undesired side effects, such as addiction and ineffectivity, and may lead to functional deficiencies of food components. So there is a need for a pharmaceutical or nutritional formulation that helps prevent or treat these disorders and does not result in these side effects.

[0007] Sandyk, R., reported in *Intern. J. Neuroscience*, 1992, **67**, 127-144 that several, but not all, of these disorders were associated with decreased serotonin levels in the brain and

reviewed some of the relevant literature about the use of tryptophan to restore serotonin levels in the brain.

[0008] We believe, however, that all these disorders are associated not only with a disorder in serotonin levels, but also with the melatonin levels in the brain, the presence of pterines and folate in the brain and the functioning of the methylating system in the body. The latter may become evident by abnormal systemic adenosine levels. Because relatively very little serotonin or melatonin is present in the normal diet, most endogenous amounts must originate from biosynthesis. An increase in the brain levels of both serotonin and melatonin can therefore only be achieved by increasing the metabolic capacity of the serotoninergic neurons. An increase of the brain levels of both serotonin and melatonin and the presence of reduced folic acid and pterins in the brain would lead to a relief of the clinical problems.

[0009] Sandyk disclosed that in some cases administration of an effective amount of the natural precursor of serotonin, tryptophan, could lead to increased levels of serotonin in brain tissue. This idea was also subject of a number of other publications, which appeared in the past.

[0010] WO 87/01590 (= EP-A-238533, Kreitzman) discloses a slimming diet for adults that provides per day less than 1000 kcal (so less than 14 kcal/kgbw.d; less than 700 kcal/day is preferred), less than 100 g protein (which results in less than 1.4 g protein per kgbw per day for a 70 kg person; always more than 30 g and less than 46 g protein is preferred) and more than 0.5 g tryptophan (more than 3 g is preferred). The product is unsuitable for feeding infants due to too high protein levels and potential toxicity of the amount of tryptophan that is included. The product should also not be used for combating obesity of the infant.

[0011] EP-A-007691 (Wurtman) discloses a formula for suppression of appetite for carbohydrates in adults, which comprises tryptophan, in an amount of 10-100 mg per kgbw.d, and carbohydrates, but no branched-chain amino acids. The ratio of the amounts of tryptophan and carbohydrates in the formula must be 1: 3-50. The product is unsuitable for use in infants, because infants require branched chain amino acids at young age for growth.

[0012] WO 91/10441 (= EP-A-463154) discloses compositions comprising polypeptides containing more than 2.2% tryptophan as well as arginine or ornithine for providing a "serotinergic effect". The product is developed for combating obesity in adults and treating

feelings of depression. Preferably α-lactalbumin is used as a source of tryptophan, which possesses a high ratio of tryptophan to large neutral amino acids plus methionine. Vegetable proteins are suggested as attractive ingredients, because of their relatively high amount of arginine and relatively low levels of phenylalanine and tyrosine. The latter two amino acids are however essential amino acids and recommended daily intakes should be ensured.

[0013] WO 98/14204 discloses the use of α-lactalbumin as nutritional complement or medicine for regulating sleep, especially when a jet lag is observed. Consumption of 100 mg and 250 mg α-lactalbumin is claimed to be effective in adults. No relation is made to use in infants nor is indicated that vitamins might play a role in regulating sleep. Alpha-lactalbumin was shown to have a value of the ratio of tryptophan to the sum of the large neutral amino acids is about 0.074 and that of the ratio Cys to Trp equals about 1.47, while the amount of tryptophan is relatively high (about 3.0%).

[0014] Heine discloses the use of hydrolysed α-lactalbumin as protein source in infant formulae in DE-A-4130284. Use of this protein hydrolysate was claimed in order to achieve a clear separation with β-lactoglobulin and thus administer a better-balanced composition with regard to threonine, tryptophan and cysteine/cystine. No reference was made to specific positive effects that can be obtained by using intact α-lactalbumin with regard to feelings of well-being nor the support of insufficiently functioning metabolic systems by using the products of the invention. No indication is given that folic acid, vitamin B12 and B6 play a crucial role in these respects. The products disclosed by Heine are also more expensive and have a worse taste compared to the products of the present invention.

[0015] After consumption of carbohydrates, insulin is released from the pancreas. This latter component is known to reverse the catabolic processes in the body, that may have resulted from a period of starvation prior to the (re)feeding of the child, into anabolic processes. As long as sufficient glucose is present in the plasma, plasma insulin levels remain sufficiently high to prevent catabolism of (in particular muscle) tissue and the resulting release of branched chain amino acids (BCAA, valine, isoleucine and leucine). In a further aspect, the invention is therefore aimed at developing formulae that provide an insulin response on a short term, with a sufficient longer-term effect as well.

[0016] Infants, especially those of young gestational age, are extremely sensitive to consumption of excess amounts of food components and imbalances in the consumption

pattern of these components, predominantly due to their low relatively metabolic and clearance capacity. This is caused by inherited problems and immaturity of their enzymatic systems and the small capacity of their organs. Infants are also sensitive to imbalances in neurotransmitter levels in the brain. It is therefore dangerous to transfer concepts that are developed for healthy adults to infant formulae. The composition of human breast milk is therefore mostly taken as "golden standard". In another aspect of the invention, a nutritional product is aimed at that does not cause any toxic reactions in normal use and to deviate as little from the golden standard as is justified.

[0017] It is important to recognise that all the aspects as mentioned above must be achieved at the same time, in order to improve well-being satisfactorily without causing negative effects to the child. Also elderly people may suffer form an imparted metabolic capacity and especially the group having neurodegenerative disorders should not be exposed to inbalanced food.

[0018] According to the prior art, relatively high doses of tryptophan have to be administered, optionally in the relative absence of large neutral amino acids and accompanied with digestible carbohydrates, in order to see clinical benefits. This approach leads to several problems. In some patients no or very little effect is observed. Administering high doses of tryptophan may lead to undesired side-effects, especially in those patients that have a low metabolic capacity or are deficient in certain vitamins or minerals. Examples of these patients are persons that are at risk for or are suffering from diabetes mellitus or bladder cancer, persons that are subjected to drug therapy, persons suffering of renal problems, young infants and elderly persons. Also, it appeared to be very difficult to estimate for a particular person the exact requirement of tryptophan for obtaining optimal serotonin levels and it is unknown how high these desirable serotonin levels are.

[0019] It has now been found that the restoration of the patient's capacity to metabolise tryptophan to serotonin and especially melatonin, is an approach that does not demonstrate the above-mentioned disadvantages. It allows the natural mechanisms to regulate endogenous levels, without subjecting the organism to high levels of potentially toxic tryptophan.

[0020] This can be achieved by administering extra amounts of certain cofactors, at least folic acid, vitamin B12 and vitamin B6. In this situation it is often not required to supplete tryptophan; however, in those cases that persons are deficient in tryptophan,

administration of relatively little amounts of tryptophan already gives significant improvement of the clinical symptoms.

[0021] In cases where a patient has a limited capacity for serotonin biosynthesis, e.g. by damage to tissue that is rich in serotoninergic neurons or due to an inherited disorder, administration of cofactors appeared to increase serotonin and melatonin levels in the brain, if a certain basal level of tryptophan was available.

[0022] It was found that the cofactors of interest are at least folic acid, pyridoxal phosphate and vitamin B12 or their functional equivalents. In addition it may be required to administer riboflavin, thiamine and niacin, or their functional equivalents.

[0023] The biochemical roles of folic acid, vitamin B6 and B12 are described in the art. To the best of the knowledge of the inventors, it is nowhere described or indicated that consumption of the combination of these vitamins, in amounts as given in the claims, is crucial for increasing well-being and normalising behaviour, senses of pain, and mood of the infant, and elder persons. It was found that the restrictions in protein and carbohydrates composition, that are present for infant formulae, necessitate the increase in these vitamins in order to have an optimal effect. It is also not earlier disclosed that inclusion of these vitamins in the amounts as claimed, significantly enlarges the group of infants that benefit from such infant formulae, especially with regard to increase of well-being, the improvement of other serotonin or melatonin-mediated disorders.

[0024] *Also, the amounts of all three essential vitamins, being folic acid, vitamin B6 and B12 are insufficient to support biosynthesis and metabolism, including the serotonin metabolism, in the young child.*

Detailed description of the invention

[0025] The characteristics of the composition according to the invention are described in the claims and in more detail below. For optimal effectivity at least 200 μg folic acid, at least 1.9 μg vitamin B12 and at least 0.3 mg vitamin B6 is required per daily dosage, and preferably at least 300 μg, at least 4.8 μg and at least 3.0 mg of respectively folic acid, vitamin B12 and vitamin B6.

[0026] In most cases also at least 0.5 mg riboflavin (vitamin B2), 1.0 mg thiamine (vitamin B1) and at least 2 mg niacin per daily dosis is required. Deficiencies on the latter components occur relatively often in the above-mentioned groups of patients and these will lead to imparted generation of ATP and reducing power in the form of NAD(P)H.

Riboflavin is also required for activating pyridoxal. Low ATP levels are deleterious to the metabolic capacity to methylate and the biosynthetic capacity for melatonin and serotonin.

[0027] It is further highly desirable that digestible carbohydrates that can serve as glucose source are included in the product. Examples are glucose polymers, lactose and sucrose. This ensures a continuous supply of reducing equivalents in the form of NADH and improves in some instances the transport of tryptophan from blood into the brain. A product according to the invention should advantageously comprise at least 5g digestible carbohydrates and preferably more than 10g on a daily basis. Per 100 kcal (419 kJ) of product, the amount of digestible carbohydrate is in the range of 4-25 g, preferably 6-22 g.

[0028] The product should further preferably comprise magnesium to improve methylation, and zinc to improve total metabolism of sulfur amino acids. Magnesium also stabilises the NMDA receptor. An overstimulation of the NMDA receptor is associated with many of the above-mentioned disorders and maintenance of an overstimulation of this receptor is claimed to aggravate some of the symptoms that are observed in some of these diseases. Zinc is further involved in the modulation of neurotransmitter receptors. Zinc should best be above 0.7 mg/100 kcal, which results in a daily intake of at least 3.6 mg. Magnesium should best be included in an amount of at least 5 mg /100 kcal, leading to a daily consumption of at least 36 mg. On the other hand, the amounts of calcium and phophorus should not be too high. Specifically, the weight ratio of Mg + Zn to Ca should be more than 0.08, preferably more than 0.10, and the weight ratio of Mg + Zn to P should be more than 0.2, preferably more than 0.26 (and Ca+ Mg + Zn / P > 1.9).

[0029] Tryptophan can be included in an amount of 0.05-3g per daily dose, in particular 0.3-1.2g. Preferably tryptophan is supplied in the form of a protein. The protein must have an amino acid composition that is characterised by a high ratio of tryptophan/ large neutral amino acids, preferably in the range of 0.048-0.2. Alfa-lactalbumin was found to be a suitable protein.

[0030] It is also advantageous to include melatonin in the product, especially in those products that are meant to be used in the evening. Melatonin upregulates certain enzymes that play an important role in the detoxification of radicals that are created in the highly firing neurons and that may play a role in the pathogenesis of the disorders mentioned above. Melatonin also can help to set and regulate the circadian rhythm, which can be very helpful in the treatment of sleeping disorders and depression. Melatonin can be included in an amount of 0.5-5g per daily dosage.

[0031] Also adenosine can be used to set the circadian cycle; an amount of 50 – 1000 mg per daily serving is recommended.

[0032] Betaine, choline, methionine or their functional equivalents should be included in those situations that is suspected that the patient suffers from a lack of food components that provide methyl groups. Examples are the elderly or schizophrenic patients that often have very poor eating behaviour. Betaine is the preferred source because it also can serve as a precursor for choline that is useful for synthesis or myelin or repair of damaged neurons and because it has an excellent taste. Obviously also choline itself can be used. Betaine can be included in an amount of 30-4000 mg and preferably 50-600 mg per daily dosage.

[0033] Methionine can be included in an amount of 50-1000 mg and preferably 100-500mg per daily dosage. Vitamin K (phylloquinones, menaquinones and other naphthoquinones) or its functional equivalent is preferably included at a level of at least 8 μg, preferably at least 30 μg per 100 kcal. For elderly persons, a daily minimum of 1 mg is found to be beneficial.

[0034] Other minerals, trace elements and vitamins can be included in amounts that comply with the recommendations as set by the National Research Council (US) or other official institutes.

[0035] The preferred amounts of all components depend on the group of patients for which the product is developed. Young infants would normally require lower amounts than adults; elderly suffering from a severe form of Alzheimer would normally benefit from less of the active components than a young adult that is suffering from the syndrome of Gilles de la Tourette.

[0036] Typical amounts per 100 kcal of the product are summarised in Table 1.

Table 1

Component	Amounts per 100 kcal product		
	Range	Preferred range	
Digestible carbohydrates	4-25	6-22	g
Folic acid	44-4000	50-2000	μg
Vitamin B12	0.8-2000	1-1000 *	μg
Vitamin B6	50-10000	60-2000	μg
Riboflavin	0.08-20	0.14-6	mg
Thiamine	55-8000	70-4000	μg

Niacin	0.55-60	1.4-25	mg niacin equivalents
Vitamin K	> 8	30-90	µg
Taurine	5-100	7-50	mg
Betaine	50-4000	30-600	mg
Magnesium	5-400	8-200	mg
Zinc	0.8-100	1-30	mg
Mg+Zn/Ca	> 0.08	> 0.10	m/m
Mg+Zn/P	>0.20	> 0.26	m/m
Melatonin	30-3000	60-800	mg
Tryptophan	0.05-8	0.2-2 *	g
Adenosine	1-1000	50-500	mg
Methionine	50-1000	100-500	mg

Note *: higher doses should preferably be given as a multifold of smaller doses.

Infant formulae

[0037] Energy density: The energy density of the product is similar to that of prior art products and is in the range of 62-73 kcal/100ml liquid or reconstituted product. Preferably the energy density is in the range of 64-71 kcal/ml.

[0038] Proteins: Protein levels in a product can be determined with the classical Kjeldahl method. The result reflects the crude proteins that are present. For the purpose of this invention we define the protein level as the amount of real proteins plus the amount of amino acids, their salts and peptides; so non-protein nitrogen is excluded. In the products of the invention the protein levels will be in the range of 1.0-3.0 g per 100 kcal, especially between 1.0 and 2.4 g/100 kcal, which allows complete satisfaction of the infants protein needs. An amount of 1.5-2.2 g/100 kcal is most preferred. The higher protein levels, such as from 2.0 or from 2.4 to 3.0 are especially suitable in combination with increased levels of folic acid, vitamin B6 and/or vitamin B12. Conventional proteins like those from cow's milk or soybeans can be used as basic protein sources, as they provide sufficient amounts of all essential amino acids but also branched-chain amino acids.

[0039] In order to increase the amount of L-tryptophan in the product, free L-tryptophan, or a functional equivalent thereof like tryptophan salts or tryptophan-rich peptides, can be suppleted. If free L-tryptophan is used, special care is taken to remove all impurities that might cause toxic reactions. It is further preferred to use a tryptophan source that is stable under the conditions that the infant formula is manufactured. A suitable source is a tryptophan-rich protein or a hydrolysate or extract thereof. If proteins are used as

ingredient, it is obvious that the levels of the large neutral amino acids (Tyr, Phe, Val, Leu, Ile) and threonine are relatively low. However they should not be that low, that the recommended daily intakes are not met. Examples of suitable proteins in this respect are acid whey, α-lactalbumin, egg protein and proteins from meat and wheat, and mixtures of two or more of these components. Acid whey protein or unhydrolysed α-lactalbumin are especially preferred, because of the excellent amino acid profile and the sustained release pattern in young children compared to hydrolysates thereof or compared to a combination of mixtures of alternative dairy products and suppleted sources of tryptophan, cysteine or arginine. Tryptophan should be present in the product in an amount of 1.6-3.5 g, especially 1.7-3.5 g per 100 g of the total protein component and preferably in an amount of 1.9-2.8 g/100 g protein.

[0040] The value of the ratio of the amounts in the product of tryptophan and the sum of the large neutral amino acids must be in the range 4.8-10 and preferably in the range 5.5-8.5 /100, and most preferably 6.2-8.2 /100. When threonine is also considered as a large neutral amino acid, the value of the ratio must be in the range 4.1-8.0 and preferably in the range 4.7-7.5.

[0041] In order to ensure sufficiently high levels of cysteine, whey proteins or egg proteins can be included in the formula. If whey proteins are used, acid whey is recommended, in order to avoid too high threonine levels. It is especially preferred to have a relatively high ratio of Cys/Trp in the range of 0.8-1.4, in order to support optimally inclusion of cysteine in liver proteins and in glutathione, which is required for optimal growth and immune function.

[0042] In order to increase insulin response arginine or lysine can be supplied as L-forms of the free amino acid or as their functional equivalents. Functional equivalents of amino acids can for example be their salts, synthetic peptides, or proteins that are rich in the particular amino acid, or extracts or hydrolysates of these proteins. Also mixtures of proteins can be included. For example mixtures of 40% casein and 60% whey could be suppleted with the hydrochloric salts of L-tryptophan or L-arginine. It is however preferred to include arginine in a form that is slowly released such as by using a granulate or similar system that comprises an arginine salt like L-arginine.HCl, or by using partially pea protein, or a hydrolysate or extract thereof, in order to extend the insulin effect. The total amount of arginine plus lysine should exceed 200, preferably exceed 250 mg/kg, e.g. 280 mg/kgbw.d. The amount of protein that is required for providing this amount of arginine

can be calculated from this number and the concentration of arginine or lysine in this protein.

[0043] Carbohydrates: According to the invention, the amount of carbohydrates in the formula must be in the range of 9-15 g/100 kcal (35-60 en%), and preferably in the range of 11-14 g/ 100 kcal. This results in a carbohydrate content of 5.7-10.5 g per 100 ml of liquid or reconstituted product. The ratio of the amount of carbohydrates to the amount of tryptophan will exceed 20 and preferably 50, and go up to 940, preferably up to 450. The weight ratio of carbohydrates to protein is preferably from 5 to 14, most preferably from 6 to 12.

[0044] It is preferred to use, at least partly, maltodextrins, apart from the lactose that may be present in the formula. This will ensure a fast availability of glucose units in plasma and therefore a fast insulin response. However, it is preferred to include at least 50% of the carbohydrates as lactose, except in those cases that the product will be used by lactose-intolerant infants. If maltodextrins are used it is advantageous to use maltodextrins having a degree of hydrolysis of 10-15 dextrin equivalents, in order to decrease the sweetness of the product.

[0045] Folic acid: Folic acid can occur in nature in many forms. Typically it is suppleted to infant formulae as monoglutamate. Though according to the invention basically all functional equivalents of folic acid can be used, it is preferred to use the monoglutamate form for obtaining best bioavailability. It is essential to include at least 44 μg per 100 kcal. If higher amounts of folic acid are consumed, a larger group of infants will show an improved serotonin- and melatonin metabolism, even if the amounts of tryptophan are relatively low as in conventional infant formulae. This is especially true if the amount of folic acid is above 50 μg per 100 kcal and sufficient vitamin B12 is made available, as is the case when the formula is suppleted with more than 0.6 μg/ 100 kcal, as is indicated below.

[0046] Vitamin B12: Vitamin B12 is normally present in infant formula partially as a complex with dairy proteins and predominantly as suppleted cyanocobalamine. Before it is absorbed the complex has to be split in the stomach and the released cyanocobalamine has to bind to a factor that is released from the stomach. Once absorbed, cyanocobalamine or alternative forms have to be converted to methylcobalamine, before they can be used as a cofactor that catalyses the conversion of homocysteine to methionine. Both absorption and conversion of cyanocobalamine occur ineffectively in part of the population of young

infants.

[0047] According to the invention it is therefore required to supplete at least 0.1 μg, and preferably more than 0.8 μg vitamin B12 per 100 kcal, preferably as hydroxycobalamine or a stabilised form, in order to support serotonin biosynthesis and metabolism effectively. Instead of vitamin B12, metabolic equivalents, i.e. compounds that lead to endogenous formation of vitamin B12, can also be used.

[0048] When indigestible carbohydrates are added to the product or other bifidogenic measures are taken, these are selected in such a way that the biosynthesis capacity of the gut flora is not imparted or even is stimulated.

[0049] Vitamin B6: Vitamin B6 is active in the cells as pyridoxal phosphate. However pyridoxine or pyridoxamine are frequently used as source of this vitamin, because of the stability of these compounds. Infants, especially those of young age, have a restricted capacity to convert these compounds to the active form. It has been found that a simple increase in the dose may decrease the intracellular pyridoxal phosphate levels. It is therefore preferred to include in the formula 50-130 μg vitamin B6 per 100 kcal. If higher amounts of vitamin B6 are suppleted, it is not recommended to use pyridoxine. Also mixtures of pyridoxamine or pyridoxal can be used.

[0050] Zinc: It is desirable that the amount of zinc is in the range of 0.7-2 mg/100 kcal, preferably from 0.7 to 1.0 mg/100 kcal. Zinc can be included as a zinc salt, such as zinc chloride or as a complex with amino acids or other components.

[0051] Niacin equivalents: Niacin functions in the human body as precursor of NAD and can be synthesised from tryptophan in the adult liver. This predominantly occurs when excess tryptophan is present. Thus tryptophan can also be used as a niacin equivalent (60 mg Trp = 1 niacin equivalent). Biosynthesis of niacin is supported in the young child by the characteristic features of the composition as claimed. This permits the availability of sufficient niacin to support the metabolic processes in the child. These can be further supported by increase of the included amount of niacin to a level of 1.2-5 mg/100 kcal.

[0052] Apart from the essential components as indicated above, other microingredients may advantageously be included in a complete infant formula, according to EEC 91/321 or corresponding Regulation: these include: Betaine, choline; taurine, inositol, calcium, phosphorus, magnesium, iron, manganese, copper, iodine, sodium, potassium, chloride. selenium, fluoride, carnitine, nucleotides, cholesterol, vitamin A, vit. D, vit. E, vit K, thiamine, riboflavin, pantothenic acid, biotin, and ascorbic acid.

[0053] Fats are included in the range of 40-57 en%. The composition of the fat can be selected from prior art compositions. Specially preferred are the ones that are disclosed in any of the earlier patents of patentee, e.g. EP-A-404058, EP-A-231904, EP-A-784437 and DE 19644518, which are incorporated by reference. The essential fatty acids that are present must preferably have the cis-configuration. Alpha-linolenic acid (=ALA): 1.75-4.0 % and linoleic acid (LA): 8-35% of total fatty acids; the ratio LA/ALA = 5-16.

[0054] The product of the invention can have the form of liquid or a powder, that can be reconstituted with water to produce a ready to feed formulation. It can also have the form of a meal that is used for weaning purposes or similar product evident to a person skilled in the art. The liquid products can be packaged in bottles, cartons and the like. The powdered products can be packaged in vacuumised packs, cans or sachets and other suitable forms that are known to a person skilled in the art.

[0055] It has been found that daily consumption of the infant formulae as described above results in the benefits as described below:

- improves feelings of well being by the infants,
- supporting regular eating and sleeping patterns
- helps to compensate for insufficient capacity of the metabolic systems, especially in the young infant
- consumption of these formulae results in plasma levels of amino acids that are more similar to those of infants, that are exclusively fed with human breast milk, compared to consumption of conventional formulae
- does not give negative side effects to the infant
- therefore improves health and immune status and supports growth of high quality
- has an excellent taste and can be produced at acceptable costs.

Examples

Example 1

A liquid infant formula having the composition as presented in table 2 was prepared.

Table 2: Composition of liquid infant formula
Values are in mg per 100 ml, except where indicated differently.

Protein (60% sweet whey, 40% casein)	1400
Added Trp	10
Added Arg	10
Lactose	7500

Table 2 (continued)

Maltodextrins (10-15 DE)	1600
Fat (EP-231904)	3100
Na	18-25
K	60-100
Cl	40-60
Ca	50-85
P	20-50
Mg	4.5-6
Fe	0.5-0.9
Zn	0.6-1.3
Cu	40-60 µg
Mn	5-20 µg
Se	1.5-2.2 µg
I	5-15 µg
Vitamin A	80-90 RE
β-Carotene	0-40 µg
Vitamin D	1-1.6 µg
Vitamin E	0.8-1.4 mg TE
Vitamin K	4-20 µg
Thiamine	35-45 µg
Riboflavin	110-150 µg
Niacin	0.7-1.0 mg NE
Pantothenate	0.25-0.35
Biotin	1.5-1.7 µg
Ascorbic acid	5-10
Taurine	4-7
Folic acid (added as monoglutamate)	25-32 µg
Vitamin B12 (added as hydroxycobalamine)	0.4-0.7 µg
Vitamin B6 (added as pyridoxine)	50-65 µg

This product can be used for improving sleeping behaviour of young infants.

Example 2

Product to be used for the elderly or toddlers as a bedtime drink:

Powdered supplement packed in a can under nitrogen; 10 g to be reconstituted in fruit juice or milk before going to bed.

To 8 kg maltodextrin DE19 are added:

2.0 kg alfa-lactalbumin

50 mg melatonin

100 mg folic acid monoglutamate

25 mg cyanocobalamin

100 mg pyridoxal

100 mg riboflavin

60 mg thiamine.HCl

30g zinc chloride.12H2O

A proper aliquot is filled in the can, e.g. 400 g.

Example 3

Product to be used for ADHD infants or Alzheimer patients

Powdered product packed in a 10g sachet. The sachet is to be mixed with a portion of breakfast cereal and reconstituted in milk.

The powder is obtained by mixing:

9.5 kg Maltodextrin
100 mg folic acid
25 mg vit. B12
100 mg B6
100 mg B2
60 mg B1
1.0 g niacin
100 g betaine
300 g magnesium chloride
30 g zinc chloride
50 g adenosine
100 mg Vitamin K

Claims

1. Use of folic acid, vitamin B6 and B12 or their functional analogues in the manufacture of a pharmaceutical composition for improving senses of well-being, control of feeling of pain and improvement of mood, sleeping behaviour, or treatment or prevention of other serotonin- or melatonin-mediated disorders.

2. Use according to claim 1, in which the composition is a composition for complete nutrition.

3. Use according to claim 2, in which the composition is a composition for complete nutrition of infants.

4. Use according to claim 2, in which the composition is a composition for complete nutrition of diseased or elderly persons.

5. Use according to any one of claims 1-4, in which the composition contains more than 44 μg of folic acid and more than 0.8 μg of vitamin B12 and more than 50 μg of vitamin B6 per 100 kcal.

6. Use according to any one of claims 1-5, in which the composition further contains at least 0.55 mg of niacin equivalents an/or at least 0.08 mg of riboflavin and/or at least 55 μg of thiamine per 100 kcal.

7. Use according to any one of claims 1-6, in which the composition further contains more than 50 mg of choline or betaine or the sum thereof, and/or at least 5 mg of taurine, and/or at least 50 mg of methionine per 100 kcal.

8. Use according to any one of claims 1-7, in which the composition further contains 0.05-8 g of tryptophan and/or 30-3000 mg of melatonin and/or 50-1000 mg of adenosine per 100 kcal.

9. Use according to any one of claims 1-8, in which the composition further contains 5-400 mg magnesium and/or 0.7-100 mg zinc per 100 kcal, the weight ratio of magnesium plus zinc to calcium being higher than 0.08.

10. Use according to any one of claims 1-9, in which the composition contains 9-15 g of carbohydrates per 100 kcal.

11. Use according to claim 1, in which the composition is a supplement for diseased or elderly persons.

12. Use according to any one of claims 1-11, in which the composition contains, in a daily dosage, at least 200 μg folic acid, at least 1.9 μg vitamin B12 and at least 0.3 mg vitamin B6.

13. Use according to claim 12, in which the composition further contains per daily dosage, at least 0.5 mg riboflavin and/or at least 1.0 mg thiamine and/or at least 2 mg niacin equivalents and/or at least 0.3 g tryptophan, at least 0.5g melatonin, at least 50 mg adenosin, at least 50 mg choline and/or betaine and/or at least 100 mg methionine and/or at least 0.03 mg vitamin K and at least 5g of digestible carbohydrates.

14. A pharmaceutical composition suitable for improving senses of well-being, control of feeling of pain and improvement of mood, sleeping behaviour, or treatment or prevention of other serotonin- or melatonin-mediated disorders, the composition containing more than 44 μg of folic acid, more than 0.8 μg of vitamin B12 and more than 50 μg of vitamin B6 per 100 kcal.

15. A method of treatment for improving senses of well-being, control of feeling of pain and improvement of mood, sleeping behaviour, or treatment or prevention of other serotonin- or melatonin-mediated disorders, comprising administering to a person in need of such treatment, an amount of at least 200μg of folic acid, at least 2 μg of vitamin B12 and at least 2 mg of vitamin B6 per daily dosage.

INTERNATIONAL SEARCH REPORT

Int. Application No
PCT/NL 00/00042

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/505 A61K31/44 A61K38/41 A23L1/302

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A23L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 545 670 A (S.H.BISSBORT ET AL.) 13 August 1996 (1996-08-13) claims ---	1,15
X	DE 43 26 675 A (MEDICE CHEM.-PHARM.FABRIK PÜTTER) 16 February 1995 (1995-02-16) claims ---	1,15
X	US 5 292 538 A (S.M.PAUL ET AL) 8 March 1994 (1994-03-08) column 1, line 15-26; claims 1,6 ---	1,2,4
X	US 5 631 271 A (W.J.SERFONTEIN) 20 May 1997 (1997-05-20) claims 1,12 ---	1-3
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 April 2000	29. 05. 2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Van Moer, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int. Application No
PCT/NL 00/00042

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 721 742 A (CLINTEC) 17 July 1996 (1996-07-17) claims	1-15

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NL 00/00042

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 15 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Ir. Application No
PCT/NL 00/00042

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